REMARKS

Applicants respectfully request entry of the amendments and remarks presented herein. Claims 1-8, 10, 17-21, 23-28, and 32 stand rejected. Claims 4, 6, 14-16, 19, 21, 22, 24, 25, and 32-34 are cancelled herein without prejudice. Thus, claims 1-3, 5, 7, 8, 10, 17, 18, 20, 23, and 26-28 are pending.

Claim 1 is amended herein to recite a method for treating or preventing an autoimmune disease, a lymphoproliferative disease, or an allergy in a subject, the method comprising: (a) identifying a subject as having, or at risk of having, an autoimmune disease, a lymphoproliferative disease, or an allergy; and (b) administering to the subject an effective amount of an antibody that binds to 4-1BB and decreases the number of $CD4^+$ T cells and increases the number of $CD8^+$ T cells. Claim 3 is amended for consistency with amended claim 1, and claim 5 is amended to depend from claim 1.

Claim 18 is amended herein to recite a method for decreasing the number of $CD4^+$ T cells and increasing the number of $CD8^+$ T cells in a subject, the method comprising administering to the subject an effective amount of an antibody that binds to 4-1BB and decreases the number of $CD4^+$ T cells and increases the number of $CD8^+$ T cells. Claim 23 is amended for consistency with amended claim 18, and claims 20 and 26 are amended to depend from claim 18.

Support for the amendments to claims 1, 3, 18, and 23 can be found in original claims 4 and 19, and in Applicants' specification at, for example, Example 2 at pages 24-25. Thus, no new matter has been added.

In light of these amendments and the following remarks, Applicants respectfully request reconsideration and allowance of claims 1-3, 5, 7, 8, 10, 17, 18, 20, 23, and 26-28.

Rejections under 35 U.S.C. § 112

The Examiner rejected claims 6, 8, and 21 under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite. The Examiner asserted that the recitation of antibody "2A" in claims 6 and 21 is indefinite because the characteristics of 2A are not known. The Examiner also asserted that the recitation of "Gr-1" in claim 8 is indefinite because its characteristics are not known. In addition, the Examiner alleged that the definition of "Gr-1" in the specification is not

sufficient, because "numerous myeloid differentiation antigens are expressed on cells of the myeloid lineage."

To further prosecution, claims 6 and 21 are cancelled herein without prejudice. Applicants disagree with the rejection of claim 8. The recitation "Gr-1" is definite. One of ordinary skill would understand, in light of the specification, what is meant to be encompassed by the term, and the Examiner has not demonstrated otherwise. Applicants' specification at page 16, lines 17-21 states that Gr-1 "is a myeloid differentiation antigen expressed on cells of the myeloid lineage, and serves as a marker for granulocyte maturation." These lines of Applicants' specification also cite the 1993 Fleming et al. publication (*J. Immunol.* 151:2399-2408; reference AW on the Form PTO-1449 submitted on September 15, 2004). This reference discloses that Gr-1 is a myeloid-restricted antigen with expression restricted to mature myeloid cells. *See*, the Abstract at page 2399, and the last sentence of the first full paragraph at page 2400. Thus, the term "Gr-1" was defined at least as of 1993. Further, Gr-1 is a standard term of art in the myeloid differentiation field, as evidenced by its use in numerous scientific publications. *See*, e.g., the Cairns et al. reference (*EMBO J.* (1994) 13:4577-4586), the Shaknovich et al. reference (*Mol. Cell. Biol.* (1998) 18:5533-5545), and the Kusmartsev et al. reference (*J. Immunol.* (2000) 165:779-785), copies of which are submitted herewith. As such, a person of skill in the art reading the claims and the specification at the time Applicants filed would have appreciated the meaning of the term, and claim 8 is clear and definite.

In light of the above, Applicants respectfully request withdrawal of the rejection of claim 8 under 35 U.S.C. § 112, second paragraph.

The Examiner rejected claims 6 and 21 under 35 U.S.C. § 112, first paragraph, for alleged lack of enablement. The Examiner asserted that the "2A" antibody must be known and readily available to the public or obtainable by a repeatable method set forth in the specification. The Examiner further asserted that since each antibody is unique, the skilled artisan using methods well known in the art and the direction provided by Applicants' specification will not arrive at the specific "2A" antibody.

Again, to further prosecution, claims 6 and 21 are cancelled herein. Thus, this rejection is moot.

The Examiner rejected claims 1-3, 7, 8, 10, 17, 18, 23-28, and 32 under 35 U.S.C. § 112, first paragraph, for alleged lack of enablement. The Examiner asserted that while the specification is enabling for methods employing a 4-1BB agonist antibody, with or without an antibody that binds to Gr-1, the specification does not reasonably provide enablement for methods employing a generically recited "4-1BB agonist."

Applicants respectfully disagree. To further prosecution, however, claims 1 and 18 are amended herein to recite an antibody that binds to 4-1BB. Thus, it is believed that the rejection has been rendered moot.

In light of the above, Applicants respectfully request withdrawal of the rejection of claims 1-3, 7, 8, 10, 17, 18, 23, and 26-28, and 32 under 35 U.S.C. § 112, first paragraph.

Rejections under 35 U.S.C. § 102

The Examiner rejected claims 1-5, 17-20, 23-27, and 32 under 35 U.S.C. § 102(b) as allegedly being anticipated by U.S. Patent No. 5,928,893 (the Kang et al. patent). In particular, the Examiner alleged that "since Kang et al. teach administering an antibody of the same specificity (4-1BB) to treat the same disease (autoimmune disease), all of its relevant functional properties, such as being an agonist vs. antagonist, and the cellular mechanisms of action, are inherently the same."

Applicants respectfully disagree. To anticipate a claim, a reference must teach every element of the claim. MPEP § 2131. "A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631 (Fed. Cir. 1987). The present claims recite that an antibody that binds to 4-1BB and decreases the number of $CD4^+$ T cells and increases the number of $CD8^+$ T cells. These features are not provided by the teachings of the Kang et al. patent, and have not been demonstrated to be necessarily present in the antibodies provided therein.

First, the Kang et al. patent fails to expressly teach the specific type of antibody that is required by the present claims. Rather, the antibody disclosed by the Kang et al. patent is one that, according to the patent when referring to the antibody as an immunosuppressive agent, can

suppress various immune responses by inhibiting the function of activated T cells with blocking the 4-1BB molecule, or by removing activated T cells expressing 4-1BB molecule. *See*, column 11, lines 34-42 of the Kang et al. patent. These teachings do not provide an antibody that can decrease the number of $CD4^+$ T cells *and* increase the number of $CD8^+$ T cells. Thus, the Kang et al. patent does not directly anticipate the presently claimed methods.

Second, with regard to inherency, Applicants note that "the fact that a certain result or characteristic may occur or be present in the prior art is not sufficient to establish the inherency of that result or characteristic." MPEP § 2112 IV, emphasis in original. See, e.g., *In re Rijckaert*, 9 F.3d 1531, 1534 (Fed. Cir. 1993), in which the court reversed a rejection because inherency was based on what would result due to optimization of conditions, not what was necessarily present in the prior art, and *In re Oelrich*, 666 F.2d 578, 581-82 (CCPA 1981). See, also, *In re Robertson*, 169 F.3d 743, 745 (Fed. Cir. 1999), in which the court held a claimed product was not inherently anticipated, stating that to establish inherency, "extrinsic evidence must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill; inherency, however, may not be established by probabilities or possibilities, and mere fact that a certain thing may result from a given set of circumstances is not sufficient."

As described above, the present claims require that the antibody decreases the number of $CD4^+$ T cells and increases the number of $CD8^+$ T cells. In contrast, the Kang et al. patent provides only general statements that the anti-4-1BB antibody disclosed therein is immunosuppressive. There are no teachings that provide *which* cells are to be suppressed. Further, there are no teachings that provide that the antibody also can increase the number of $CD8^+$ T cells. The Kang et al. patent certainly does not sufficiently demonstrate that the antibody disclosed therein would necessarily have the same effect as the antibody recited in the present claims. As such, the Kang et al. patent does not anticipate the presently claimed methods, either directly or inherently.

In light of the above, Applicants respectfully request withdrawal of the rejection of claims 1-3, 5, 17, 18, 20, 23, 26, and 27 under 35 U.S.C. § 102(b).

The Examiner rejected claims 1-5, 10, 17-20, 23-28, and 32 under 35 U.S.C. §§ 102(a) and 102(e) as allegedly being anticipated by U.S. Patent No. 6,303,121 (the Kwon patent). The Examiner alleged that when two antibodies bind to the same target and are administered to the same patient population to treat the same disease, the two antibodies inherently have the same effect.

Applicants respectfully disagree. The Examiner's assertion regarding the inherent mechanism of action of the Kwon antibody is incorrect. The fact that two antibodies bind specifically to the same target, in this case 4-1BB, does not necessarily mean that both antibodies will have the same effect. Further, as stated above, the fact that a certain result or characteristic may occur or be present in the prior art is not sufficient to establish the inherency of that result or characteristic. In the present case, there is no evidence that the antibodies disclosed by the Kwon patent have the effect of decreasing the number of $CD4^+$ T cells and increasing the number of $CD8^+$ T cells, as recited in the present claims. In fact, the Kwon patent discloses that "4-1BB signal alone showed nearly no stimulatory activity in $CD4^+$ T cells of HIV-1 positive individuals," but that "$CD4^+$ T cell proliferation occurred with 4-1BB cross-linking when suboptimal stimulation through CD28 was added." Col. 26, ll. 24-32. The Kwon patent also provides data from studies of 4-1BB co-stimulation and HIV-1 production, which "suggest that co-stimulation via 4-1BB results in $CD4^+$ T cell activation . . . ." Col. 27, ll. 12-15. Further, the Kwon patent discloses that "in HIV-1 patients, $CD8^+$ T cells generally proliferate more vigorously than $CD4^+$ T cells when the cells were stimulated with anti-4-1BB mAb," and that "the stimulation index of primary $CD4^+$ T cells in response to 4-1BB co-stimulation was very low." Col. 28, ll. 39-41 and 65-67. Thus, the disclosure of the Kwon patent provides no teaching or suggestion that an anti-4-1BB antibody would decrease the number of $CD4^+$ T cells and increase the number of $CD8^+$ T cells. Further, it has not been sufficiently demonstrated that the antibody of Kwon would necessarily have the features of the antibody recited in the present claims. As such, the presently claimed methods are novel over the Kwon patent.

In light of the above, Applicants respectfully request withdrawal of the rejection of claims 1-3, 5, 10, 17, 18, 20, 23, and 26-28 under 35 U.S.C. §§ 102(a) and 102(e).

CONCLUSION

Applicants submit that claims 1-3, 5, 7, 8, 10, 17, 18, 20, 23, and 26-28 are in condition for allowance, which action is respectfully requested. The Examiner is invited to telephone the undersigned agent if such would further prosecution.

Please apply $2230 for the Petition for Extension of Time fee, $810 for the Request for Continued Examination fee, and any other charges or credits, to deposit account 06-1050.

Respectfully submitted,

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